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P2-purigenic receptors regulate phospholipase C and adenylate cyclase activities in immortalized Schwann cells.

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Schwann cells play an important role in both the development and regeneration of peripheral nerves. Proliferation and differentiation of Schwann cells are critically dependent on changes in the levels of cAMP. ATP is a fast excitatory transmitter in the peripheral nervous system, inducing depolarization of the vagus nerve through occupancy of P2-purinergic receptors. In the present study we demonstrate that extracellular ATP stimulates phospholipase C and inhibits adenylate cyclase activities in cultured Schwann cells. Addition of ATP inhibited, in a concentration-dependent manner, forskolin- or isoprenaline-stimulated adenylate cyclase activity. The rank order of potency corresponding to different purinergic receptor agonists was 2-methylthio-ATP > ATP = ADP > or = adenosine 5'-[gamma-thio]triphosphate (ATP[S]) > UTP, consistent with the involvement of a P2y subtype. Adenosine and adenosine 5'-[alpha,beta-methylene]-triphosphate (pp[CH2pA) were ineffective. Preincubation with pertussis toxin completely blocked this inhibitory effect. When Schwann cells were pre-labelled with myo-[3H]inositol and incubated in Hanks' balanced salt solution containing Ca2+ and Mg2+, addition of ATP[S] resulted in a concentration-dependent increase in the release of InsP with a concomitant increase in intracellular free [Ca2+] ([Ca2+]i). Under these conditions, the effects of both ATP and UTP were of lower magnitude. Removal of Ca2+ and Mg2+ from the assay medium resulted in a significant increase in the effects of ATP[S], ATP and UTP. The decreased response observed in the presence of both bivalent cations (1.2 mM Ca2+ and 1 mM Mg2+) could not be explained either by increased degradation of ATP by Ca2+/Mg2+-dependent nucleotidases or by cation influx. The rank order of potency for the effects of agonists on phospholipase C activity was ATP[S] = adenosine 5'[gamma-imido]triphosphate > ATP -UTP > ADP, indicating the involvement of a P(2U) receptor subtype in this response. Adenosine, AMP and pp[CH2]pA were ineffective. These results demonstrate that

immortalized Schwann cells express P(2U) and P(2Y) purinoceptors, which are coupled to stimulation of phospholipase C and inhibition of adenylate cyclase, respectively. Our observations unveil signal-transduction pathways that may be used by ATP to regulate proliferation and differentiation of Schwann cells, and ultimately to influence nerve homeostasis.

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